

d 13 1-5, 21 bib ab

L3 ANSWER 1 OF 26 MEDLINE on STN
AN 2002427395 MEDLINE
DN 22172984 PubMed ID: 12184921
TI Pre-pro-B cell growth-stimulating factor (PPBSF) upregulates IL-7Ralpha chain expression and enables pro-B cells to respond to monomeric IL-7.
AU Wei Chiju; Lai Laijun; Goldschneider Irving
CS Department of Pathology, School of Medicine, University of Connecticut Health Center, Farmington, CT 06030-3105, USA.
NC AI32752 (NIAID)
SO JOURNAL OF INTERFERON AND CYTOKINE RESEARCH, (2002 Jul) 22 (7) 823-32. Journal code: 9507088. ISSN: 1079-9907.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200302
ED Entered STN: 20020820
Last Updated on STN: 20030212
Entered Medline: 20030211
AB Although pro-B cells are well represented in **IL-7** knockout (KO) mice, they express abnormally low concentrations of the **interleukin-7** receptor alpha-chain (IL-7Ralpha) and do not generate pre-B cells. Here, we demonstrate that pro-B cells from **IL-7** KO mice can be induced to generate pre-B cells and immature B cells by exposure to recombinant **IL-7** (rIL-7) in vivo but not in vitro. Experiments in recombinant activation gene-1 (RAG-1) KO mice indicate that the in vitro unresponsiveness of **IL-7**(-/-) pro-B cells to rIL-7 is unrelated to the absence of a functional pre-B cell receptor (pre-BCR). Rather, it appears to be due to the suboptimal expression of the IL-7Ralpha chain. Thus, **IL-7**(-/-) pro-B cells readily respond to rIL-7 in vitro if IL-7Ralpha chain expression is first upregulated by exposure to **IL-7** in vivo or to **IL-7**(+/+) bone marrow (BM) stromal cells or conditioned medium (CM) therefrom in vitro. Similar results were obtained when pro-B cells from **IL-7** KO mice were cultured on **IL-7**(-/-) BM stromal cells in the presence of rIL-7. This suggested that the recently described pre-pro-B cell growth-stimulating factor (PPBSF), a self-assembling **hybrid** cytokine comprising **IL-7** and the stromal cell-derived **hepatocyte growth factor** beta-chain (HGFbeta), is required to stimulate pro-B cells from **IL-7** KO mice. This inference was verified by demonstrating that purified PPBSF upregulates IL-7Ralpha chain expression on **IL-7**(-/-) pro-B cells in vitro and enables them to respond to rIL-7 in a stepwise manner. We, therefore, postulate that PPBSF is the operative form of **IL-7** that normally induces IL-7Ralpha(lo) pre-pro-B cells to proliferate and differentiate into IL-7Ralpha(hi) pro-B cells, which then proliferate and differentiate into pre-B cells on stimulation with monomeric **IL-7**.

L3 ANSWER 2 OF 26 MEDLINE on STN
AN 2001517560 MEDLINE
DN 21448677 PubMed ID: 11564764
TI Cutting edge: Identification of a **hybrid** cytokine consisting of **IL-7** and the beta-chain of the **hepatocyte growth factor**/scatter factor.
AU Lai L; Goldschneider I
CS Department of Pathology, School of Medicine, University of Connecticut Health Center, Farmington, CT 06030, USA.
NC AI 32752 (NIAID)
SO JOURNAL OF IMMUNOLOGY, (2001 Oct 1) 167 (7) 3550-4. Journal code: 2985117R. ISSN: 0022-1767.

CY United States
 DT Journal; Article; (JOURNAL ARTICLE)
 LA English
 FS Abridged Index Medicus Journals; Priority Journals
 EM 200112
 ED Entered STN: 20010924
 Last Updated on STN: 20020122
 Entered Medline: 20011204

AB Pre-pro-B cell growth-stimulating factor (PPBSF) is a heterodimer of **IL-7** and a 30-kDa cofactor. Unlike monomeric **IL-7**, PPBSF selectively induces proliferation and differentiation of pre-pro-B cells and up-regulates **IL-7** α -chain expression. Here we clone the PPBSF cofactor from bone marrow stromal cells and identify it as a variant beta-chain of **hepatocyte growth factor (HGF)**, a pleiotropic cytokine homologous to plasminogen that regulates cell growth, motility, and morphogenesis. We further demonstrate that, in the presence of low m.w. heparin sulfate-derived oligosaccharides, rHGF β combines with rIL-7 to form a biologically active heterodimer having the properties of PPBSF. The results indicate that PPBSF is a novel form of cytokine (**hybrid** cytokine) consisting of the bioactive components of two unrelated cytokines. Based on its heparin-binding and mitogenic properties, we postulate that the HGF β -chain in PPBSF enables **IL-7** to participate in cognate interactions at the stromal cell surface and to transduce signals effectively at low levels of IL-7R.

L3 ANSWER 3 OF 26 CAPLUS COPYRIGHT 2003 ACS on STN
 AN 2002:593272 CAPLUS
 DN 137:139125
 TI Pre-pro-B cell growth-stimulating factor (PPBSF) upregulates IL-7R. α . chain expression and enables pro-B cells to respond to monomeric IL-7
 AU Wei, Chiju; Lai, Laijun; Goldschneider, Irving
 CS Dept. of Pathology, School of Medicine, Univ. of Connecticut Health Center, Farmington, CT, 06030-3105, USA
 SO Journal of Interferon and Cytokine Research (2002), 22(7), 823-832
 CODEN: JICRFJ; ISSN: 1079-9907
 PB Mary Ann Liebert, Inc.
 DT Journal
 LA English
 AB Although pro-B cells are well represented in **IL-7** knockout (KO) mice, they express abnormally low concns. of the **interleukin-7** receptor α -chain (IL-7R. α .) and do not generate pre-B cells. Here, we demonstrate that pro-B cells from **IL-7** KO mice can be induced to generate pre-B cells and immature B cells by exposure to recombinant **IL-7** (rIL-7) in vivo but not in vitro. Expts. in recombinant activation gene-1 (RAG-1) KO mice indicate that the in vitro unresponsiveness of **IL-7** $-/-$ pro-B cells to rIL-7 is unrelated to the absence of a functional pre-B cell receptor (pre-BCR). Rather, it appears to be due to the suboptimal expression of the IL-7R. α . chain. Thus, **IL-7** $-/-$ pro-B cells readily respond to rIL-7 in vitro if IL-7R. α . chain expression is first upregulated by exposure to **IL-7** in vivo or to **IL-7** $+/+$ bone marrow (BM) stromal cells or conditioned medium (CM) there from in vitro. Similar results were obtained when pro-B cells from **IL-7** KO mice were cultured on **IL-7** $-/-$ BM stromal cells in the presence of rIL-7. This suggested that the recently described pre-pro-B cell growth-stimulating factor (PPBSF), a self-assembling **hybrid** cytokine comprising **IL-7** and the stromal cell-derived **hepatocyte growth factor** β -chain (**HGF**. β .), is required to stimulate pro-B cells from **IL-7** KO mice. This inference was verified by demonstrating that purified PPBSF upregulates IL-7R. α . chain expression on **IL-7** $-/-$ pro-B cells in vitro and enables them to respond to rIL-7 in

a stepwise manner. We, therefore, postulate that PPBSF is the operative form of **IL-7** that normally induces **IL-7R.alpha.Io** pre-pro-B cells to proliferate and differentiate into **IL-7R.alpha.hi** pro-B cells, which then proliferate and differentiate into pre-B cells on stimulation with monomeric **IL-7**.

RE.CNT 47 THERE ARE 47 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 4 OF 26 CAPLUS COPYRIGHT 2003 ACS on STN

AN 2001:748030 CAPLUS

DN 135:302953

TI **Hybrid** cytokine of **IL-7** and .beta.-chain of **hepatocyte growth factor**

IN Goldschneider, Irving; Lai, Laijun

PA University of Connecticut, USA

SO PCT Int. Appl., 68 pp.

CODEN: PIXXD2

DT Patent

LA English

FAN.CNT 1

| | PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|------|--|------|----------|-----------------|----------|
| PI | WO 2001075140 | A1 | 20011011 | WO 2001-US10408 | 20010330 |
| | W: CA, JP | | | | |
| | RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR | | | | |
| | US 2002058791 | A1 | 20020516 | US 2001-823933 | 20010330 |
| PRAI | US 2000-193273P | P | 20000330 | | |
| AB | A hybrid cytokine comprising the .beta.-chain of hepatocyte growth factor and IL-7 , linked by a linker mol., having pre-pro-B growth stimulating activity. | | | | |

RE.CNT 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 5 OF 26 CAPLUS COPYRIGHT 2003 ACS on STN

AN 2001:712014 CAPLUS

DN 136:4515

TI Cutting edge: identification of a **hybrid** cytokine consisting of **IL-7** and the .beta.-chain of the **hepatocyte growth factor**/scatter factor

AU Lai, Laijun; Goldschneider, Irving

CS Department of Pathology, School of Medicine, University of Connecticut Health Center, Farmington, CT, 06030, USA

SO Journal of Immunology (2001), 167(7), 3550-3554

CODEN: JOIMA3; ISSN: 0022-1767

PB American Association of Immunologists

DT Journal

LA English

AB Pre-pro-B cell growth-stimulating factor (PPBSF) is a heterodimer of **IL-7** and a 30-kDa cofactor. Unlike monomeric **IL-7**, PPBSF selectively induces proliferation and differentiation of pre-pro-B cells and up-regulates **IL-7R.alpha.-chain** expression. Here the authors clone the PPBSF cofactor from bone marrow stromal cells and identify it as a variant .beta.-chain of **hepatocyte growth factor** (HGF), a pleiotropic cytokine homologous to plasminogen that regulates cell growth, motility, and morphogenesis. The authors further demonstrate that, in the presence of low mol. wt. heparin sulfate-derived oligosaccharides, rHGF.beta. combines with rIL-7 to form a biol. active heterodimer having the properties of PPBSF. Thus, PPBSF is a novel form of cytokine (**hybrid** cytokine) consisting of the bioactive components of 2 unrelated cytokines. Based on its heparin-binding and mitogenic properties, the authors postulate that the **HGF.beta.-chain** in PPBSF enables **IL**

-7 to participate in cognate interactions at the stromal cell surface and to transduce signals effectively at low levels of IL-7R.
RE.CNT 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 21 OF 26 USPATFULL on STN
AN 2002:113045 USPATFULL
TI **Hybrid** cytokine of **IL-7** and beta-chain of **hepatocyte growth factor**
IN Goldschneider, Irving, Avon, CT, UNITED STATES
Lai, Laijun, Newington, CT, UNITED STATES
PI US 2002058791 A1 20020516
AI US 2001-823933 A1 20010330 (9)
PRAI US 2000-193273P 20000330 (60)
DT Utility
FS APPLICATION
LREP CUMMINGS AND LOCKWOOD, GRANITE SQUARE, 700 STATE STREET, P O BOX 1960,
NEW HAVEN, CT, 06509-1960
CLMN Number of Claims: 31
ECL Exemplary Claim: 1
DRWN 26 Drawing Page(s)
LN.CNT 1256
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB A **hybrid** cytokine comprising the B-chain of **hepatocyte growth factor** and **IL-7**, linked by a linker molecule, having pre-pro-B growth stimulating activity.

=> d his

(FILE 'HOME' ENTERED AT 13:16:47 ON 13 NOV 2003)

FILE 'MEDLINE, CAPLUS, USPATFULL' ENTERED AT 13:17:03 ON 13 NOV 2003

L1 7370 S IL-7 OR INTERLEUKIN-7
L2 1092 S L1 (P) (HYBRID# OR CHIMER? OR FUSION# OR CONJUGA? OR DERIVAT?
L3 26 S L2 (P) (HGF OR HEPATOCYTE GROWTH FACTOR)

=>

s hgf or hepatocyte growth factor
L4 11566 HGF OR HEPATOCYTE GROWTH FACTOR

=> s l4 (p) (pre-pro-beta)
L5 0 L4 (P) (PRE-PRO-BETA)

=> s il-7 or interleukin-7
L6 7370 IL-7 OR INTERLEUKIN-7

=> s l6 (p) (pre-pro-beta)
L7 0 L6 (P) (PRE-PRO-BETA)

=>